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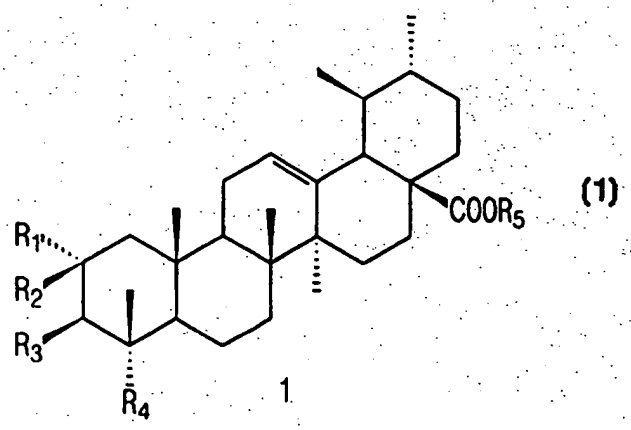
(54) Title: ASIATIC ACID DERIVATIVES AND MEDICINES FOR TREATING WOUNDS, WHICH CONTAINS THE SAME

(57) Abstract

The present invention relates to asiatic acid derivatives represented by formula (1), and medicines for treating wounds, which contains the same as an active component.



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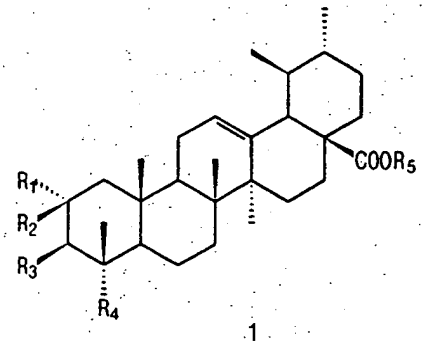
TITLE OF INVENTION

ASIATIC ACID DERIVATIVES AND MEDICINES FOR TREATING WOUND, WHICH CONTAINS THE SAME

Technical Field

The present invention relates to asiatic acid derivatives represented by following chemical formula 1:



1

wherein, R_1 represents hydrogen, hydroxy group which may be protected by acetyl or benzyl group, methanesulfonyloxy, (methylthio) thiocarbonyloxy, halogen, ethoxymethyloxy or octyloxymethyloxy group; R_2 represents hydrogen or hydroxy group; R_1 and R_2 may form an oxo group; R_3 represents hydrogen or hydroxy group which may be protected by acetyl or benzoyl group; R_2 and R_3 may form an epoxy group; R_4 represents hydroxymethyl group which may be protected by acetyl or benzoyl group; R_3 and R_4 may form $-OC(R_6)(R_7)OCH_2-$ [wherein, R_6 is hydrogen, a lower alkyl group having 1 to 4 carbon atoms, or phenyl group, R_7 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms or phenyl group, and R_6 and R_7 may form $-(CH_2)_5-$]; R_5 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms, an alkoxymethyl group having 1 to 4 carbon atoms, octyloxymethyl, methoxyethoxymethyl, benzyloxymethyl or 2-tetrahydropyranyl group; and medicines for treating wound, which contains the same as an active component.

Background Art

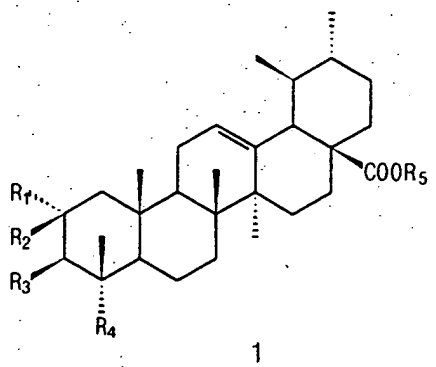
Asiatic acid, madecassic acid and asiaticoside(trisaccharide of asiatic acid), which are compounds extracted from *Centella asiatica*, were isolated firstly by Bontems in 1941 [J. E. Bontems, *Bull. Sci. Pharmacol.*, **49**, 186-91(1941)] and their structures were defined by Polonsky [J. Polonsky, *Compt. Rend.*, **232**, 1978-80(1951); J. Polonsky, *Bull. Soc. Chim.*, 173-80(1953)]. The extracts including asiatic acid and asiaticoside from *Centella asiatica* have been used for treatment of hurted skin or chronic ulcer since old times, and also for treatment deformation of skin due to tuberculosis or leprosy [P. Boiteau, A. Buzas, E. Lederer and J. Polonsky, *Bull. Soc. Chim.*, **31**, 46-51(1949)]. It is reported that the mechanism of these compounds for treating hurted skin comprises activating cells of Malpighean layer and inducing keratinization. [May. Anne, *Eur. J. Pharmacol.*, **4(3)**, 331-9(1968)]

Madecassol, a commercially available medicine for treating skin disease, also is a mixture of three components, i.e., asiaticoside (40%) with asiatic acid and madecassic acid (60%). It is known that remedial effect mainly comes from asiaticoside, trisaccharide of asiatic acid among the three components, and it is reported that asiatic acid itself has no remedial effect. [Kiesswetter, *Wien. Med. Wochschr.*, **114(7)**, 124-6(1964)] However, there has been a report proving that the above result is due to the difference in the absorption process of there compounds in body, and the material practically showing the remedial effect is asiatic acid itself. [L. F. Chasseaud, B. J. Fry, D. R. Hawkins, J. D. Lewis, T. Taylor and D. E. Hathway, Arzneim-Forsch, **21(9)**, 179-84(1971)] Thus, the synthesis and remedial effect of asiatic acid becomes the center of interest. However, total synthesis of asiatic acid requires quite many synthetic steps when starting from a simple starting material, so that the synthesis involves many problems due to its complicated process and economical disadvantage.

Disclosure of the Invention

The present inventors have synthesized various asiatic acid derivatives, starting from asiatic acid obtained from *Centella asiatica*. They also found that the derivatives have excellent effect for treating wound and completed the present invention.

The present invention relates to asiatic acid derivatives represented by following formula 1,



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wherein, R_1 represents hydrogen, hydroxy group which may be protected by acetyl or benzyl group, methanesulfonyloxy, (methylthio) thiocarbonyloxy, halogen, ethoxymethyloxy or octyloxymethyloxy group; R_2 represents hydrogen or hydroxy group; R1 and R_2 may form an oxo group; R_3 represents hydrogen or hydroxy group which may be protected by acetyl or benzoyl group; R_2 and R_3 may form an epoxy group; R_4 represents hydroxymethyl group which may be protected by acetyl or benzoyl group; R_3 and R_4 may form $-OC(R_6)(R_7)OCH_2-$ [wherein, R_6 is hydrogen, a lower alkyl group having 1 to 4 carbon atoms, or phenyl group, R_7 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms or phenyl group, and R_6 and R_7 may form $-(CH_2)_5-$]; R_5 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms, an alkoxymethyl group having 1 to 4 carbon atoms, octyloxymethyl, methoxyethoxymethyl, benzyloxymethyl or 2-tetrahydropyranyl group,

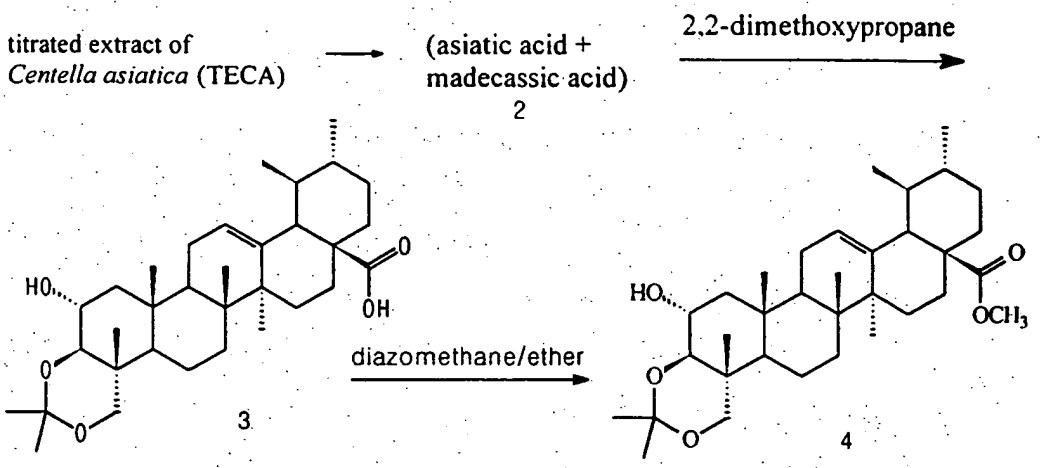
and medicines for treating wound, which contains the same as an active component.

The process for preparing the asiatic acid derivatives according to the present invention is illustrated here-in-below:

Method 1

Titrated extracts of *Centella asiatica* (TECA) is hydrolyzed to obtain a mixture of asiatic acid and madecassic acid (2), and the mixture is reacted with 2,2-dimethoxypropane in the presence of acid catalyst. The reaction product is purified by column chromatography to isolate 3,23-O-isopropylidene asiatic acid (3) in which 3,23-dihydroxy group is protected. The obtained product is treated with diazomethane to synthesize methyl 3,23-O-isopropylidene asiatate (4). [See Scheme 1.]

Scheme 1

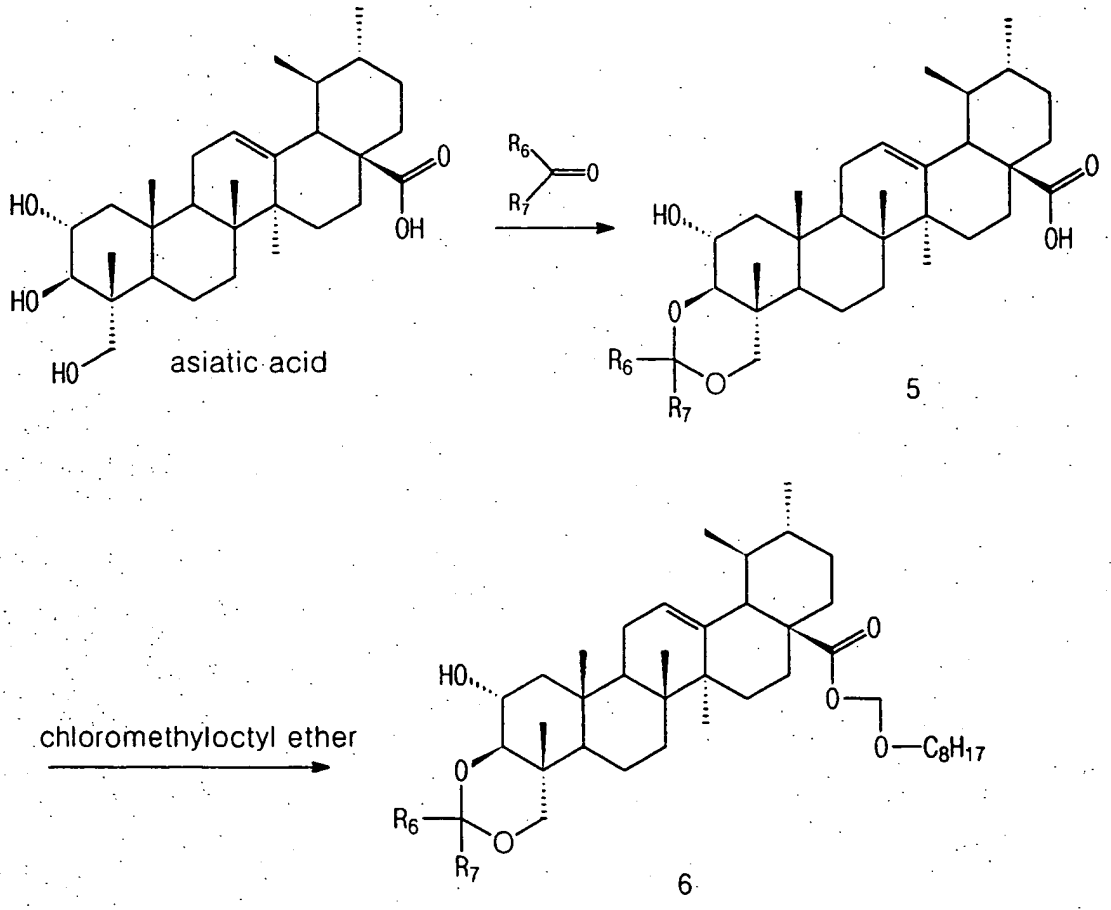


Method 2

Two hydroxy groups at 3- and 23-position of asiatic acid are protected with various ketone or aldehyde group to synthesize compounds represented by general formula (5). [Provided that R_6=H and R_7=H, the compound is synthesized by the use of dimethyl sulfoxide and trimethylsilyl chloride.] The compound of general formula (5) is treated

with chloromethyl octyl ether to synthesize a compound represented by general formula (6). [See Scheme 2.]

Scheme 2



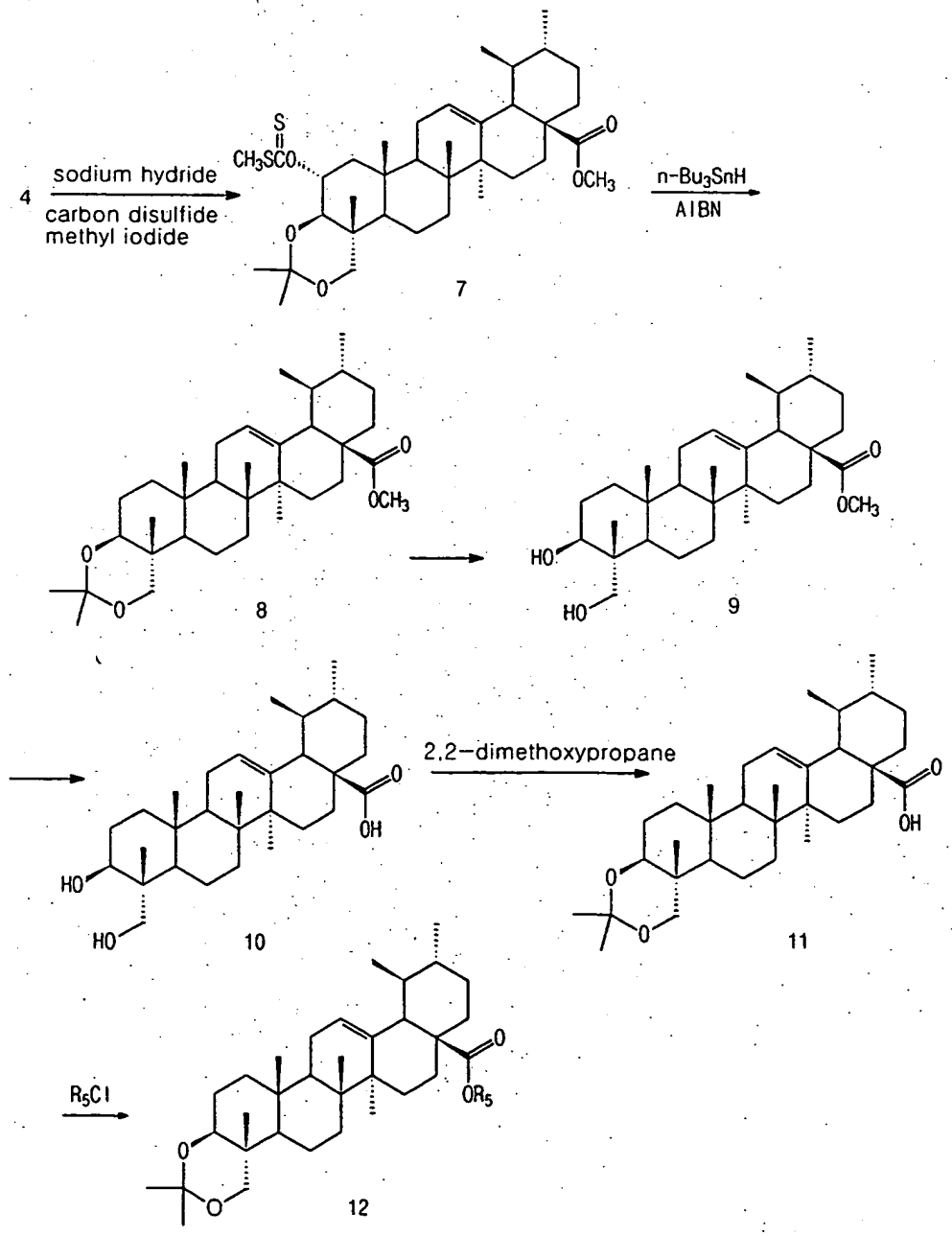
(wherein, R_6 and R_7 are the same that are defined above.)

Method 3

The hydroxy group at 2-position of compound (4) obtained above is treated with sodium hydride and imidazole, to be converted to alkoxide group. Carbon disulfide is added thereto and the mixture is heated under reflux, and then treated with methyl iodide to obtain a xanthate (7). The resultant compound is treated with tributyltin hydride and catalytic amount of AIBN to give methyl 2-deoxy-3,23-O-isopropylidene asiatate

(8), which is then deprotected to obtain methyl 2-deoxyasiatate (9). The compound (9) above is hydrolyzed to obtain 2-deoxyasiatic acid (10). From 2-deoxyasiatic acid (10), 2-deoxy-3,23-O-isopropylidene asiatic acid (11) is synthesized, which is then reacted under the condition described in Method 2, to synthesize a compound represented by general formula (12). [See Scheme 3.]

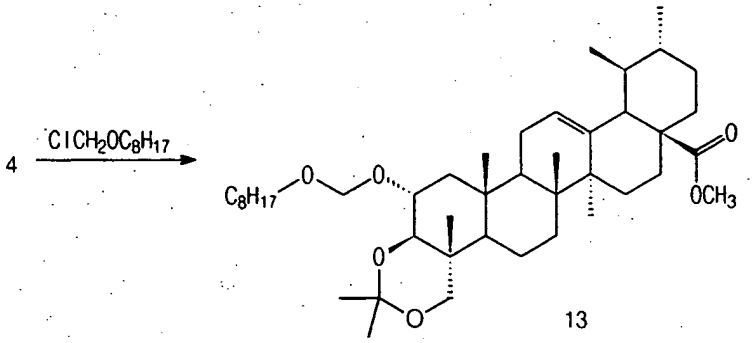
Scheme 3



Method 4

Methyl 2-O-octyloxymethyl-3,23-O-isopropylidene asiatate (13) is synthesized by means of Method 2 from compound (4) obtained above . [See Scheme 4.]

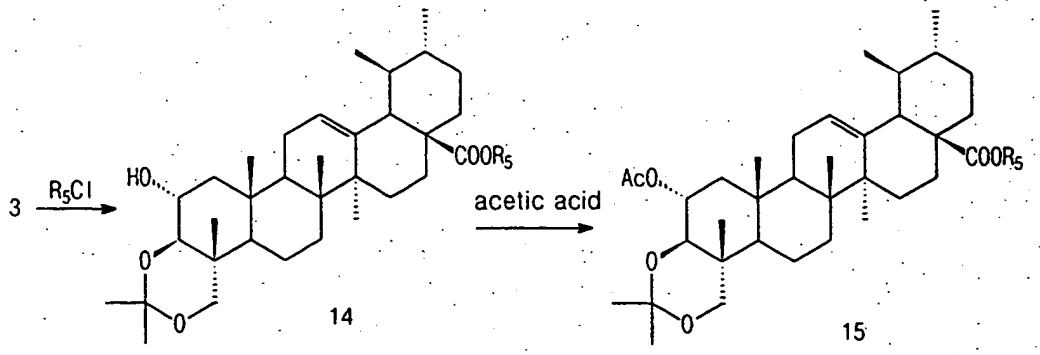
Scheme 4



Method 5

The compound (3) obtained above is reacted with an alkyl halide under the conditions of Method 2, to synthesize a compound represented by general formula (14), which is acetylated at 2-position to synthesize a compound represented by general formula (15). [See Scheme 5.]

Scheme 5

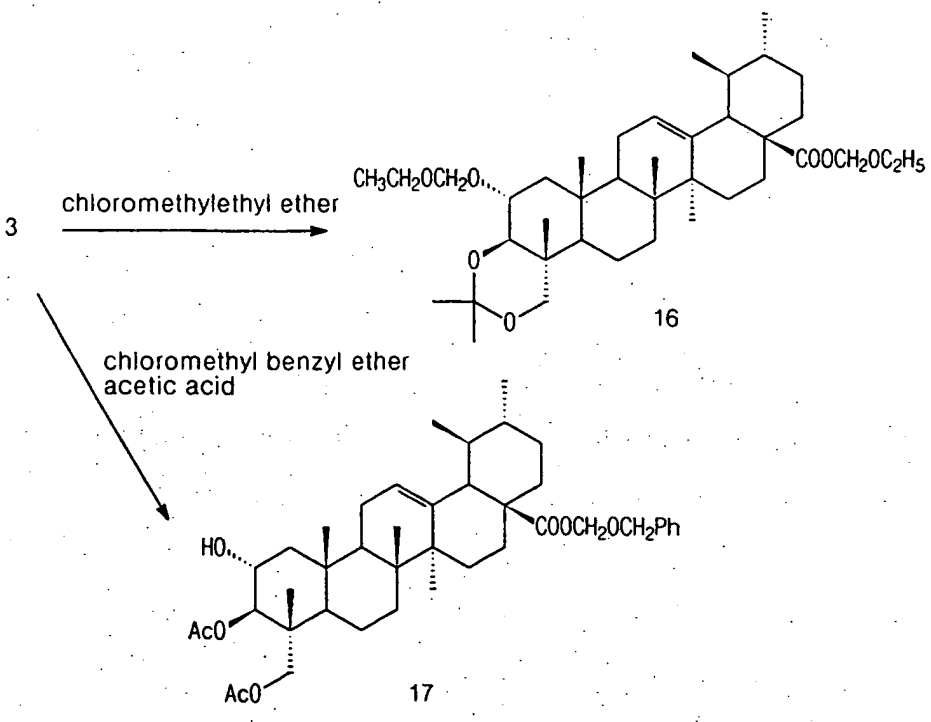


(wherein, R_5 is the same that is defined above.)

Method 6

From the compound (3) obtained above, ethoxymethyl 2-O-ethoxymethyl-3,23-O-isopropylidene asiatate (16) is obtained under the same conditions of Method 2 but with prolonged reaction time. By means of the same method, benzyloxymethyl group is incorporated to COOH group at 28-position by using chloromethyl benzyl ether. The resultant compound is acetylated to synthesize benzyloxymethyl 3,23-O-diacetylasiatate (17). [See Scheme 6.]

Scheme 6

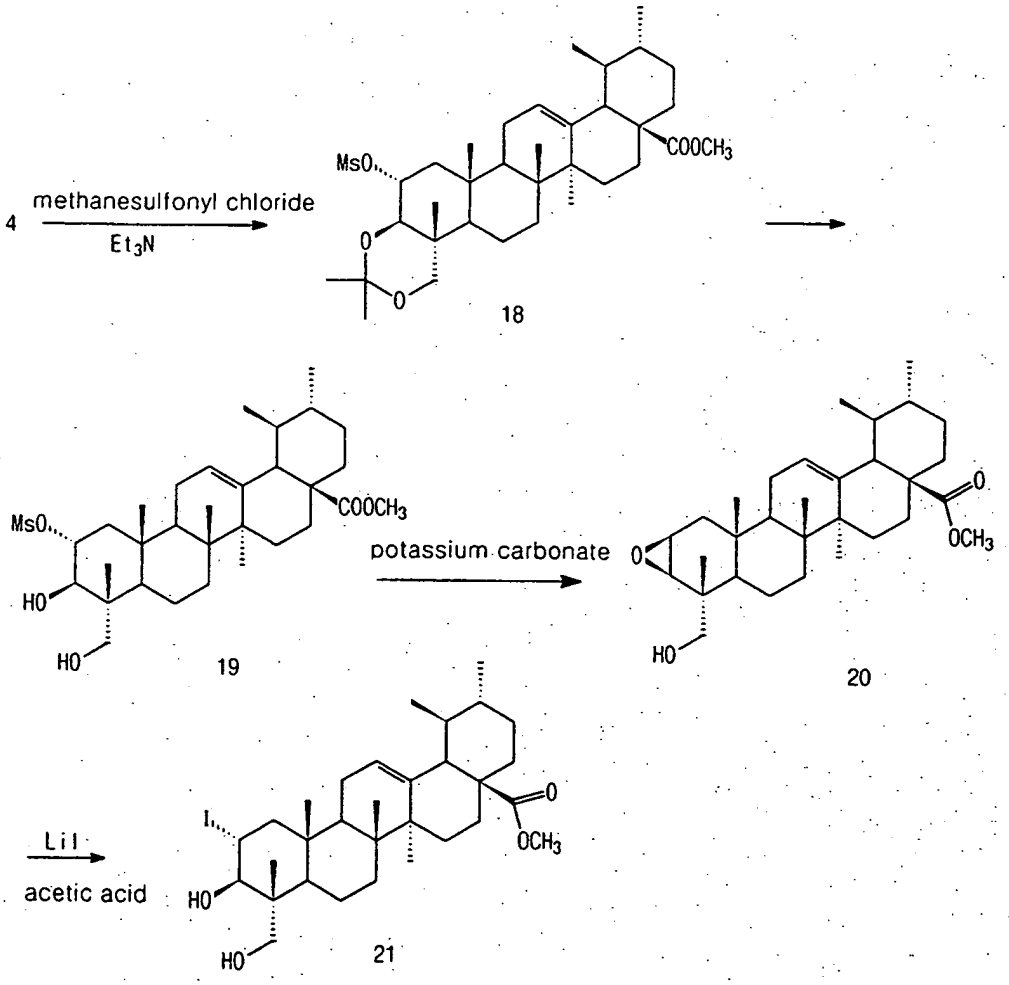


Method 7

2,3-Hydroxy group of asiatic acid is converted to 2,3-epoxy group, and the obtained compound is reacted with a variety of nucleophilic compound to cause ring opening of epoxy group to prepare a series of novel compounds according to the present invention. In other words, the compound (4) obtained above is reacted with methanesulfonyl

chloride to obtain methyl 2-O-methanesulfonyl-3,23-O-isopropylidene asiatate (18), which is then treated with PTSA to give methyl 2-O-methanesulfonyl asiatate (19). The obtained compound is then treated with potassium carbonate in methanol solvent to synthesize methyl 2,3-epoxyasiatate (20). The compound (20) is treated with lithium iodide trihydrate and acetic acid to synthesize methyl 2-α-iodo-2-deoxyasiatate (21) of which epoxide has been opened. [See Scheme 7.]

Scheme 7

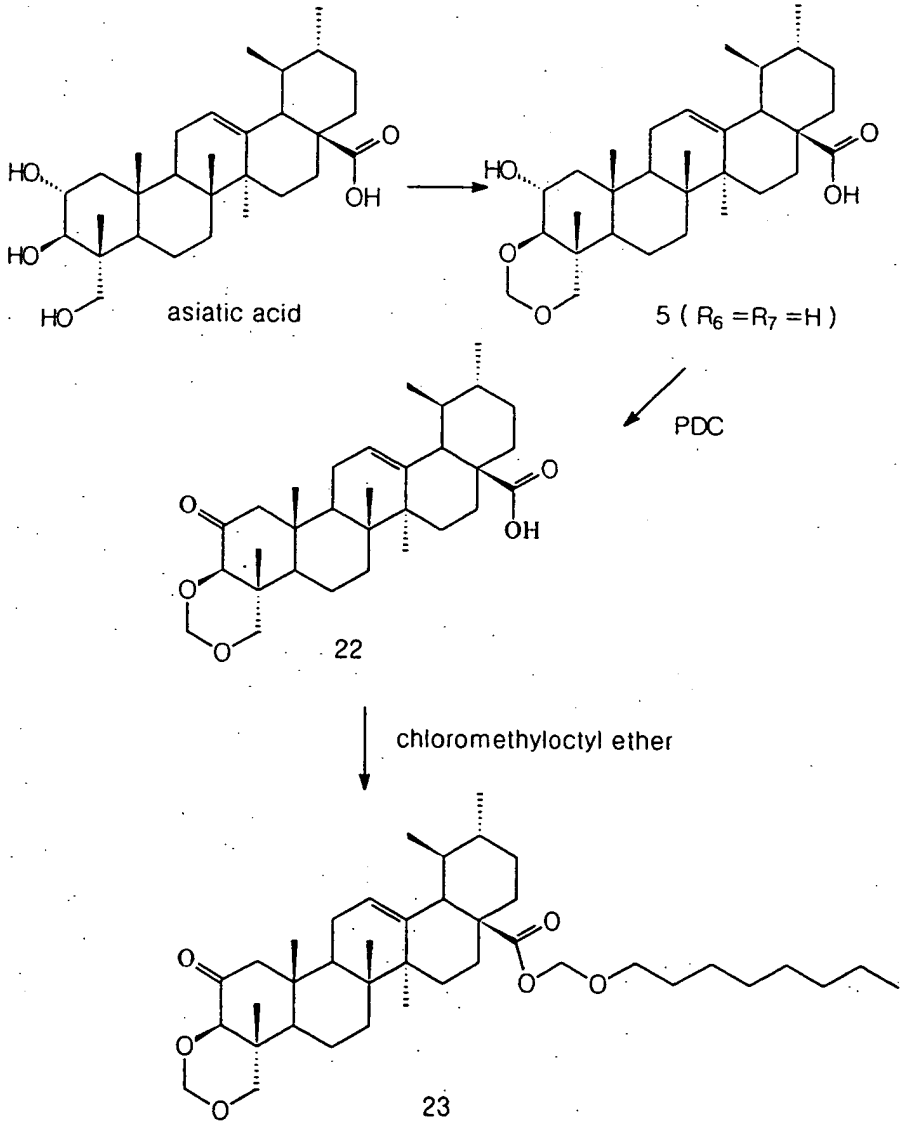


Method 8

Dihydroxy group at 3- and 23-position of asiatic acid was methylidene protected by dimethylsulfoxide and trimethylsilyl chloride to

synthesize a compound represented by general formula (5, R_6=R_7=H), which is then treated with pyridinium dichromate (PDC) to obtain a compound represented by general formula (22). The resultant compound is reacted with chloromethyl octyl ether to give a compound represented by general formula (23). [See Scheme 8.]

Scheme 8



The asiatic acid derivatives according to the present invention exhibited comparable to or more excellent effect than that of control

agent, 1% quantitative extract of *Centella asiatica* (TECA).

The dose of compound of general formula (1) is 10 to 100 mg/day for an adult. The dose usually depends on age and body weight of a patient, as well as the condition of symptoms.

The medicine for treating wound according to the present invention may be formulated into an ointment by means of conventional methods.

Best Mode for Carrying out the Invention

Now, The present invention is described with reference to Examples, Experimental Examples and Formulation Example. However, it should not be noted that the present invention is restricted to those examples.

Example 1: Isolation and purification of asiaticoside and asiatic acid in large scale

Quantitative extract (5 g) of *Centella asiatica* was directly separated by column chromatography (silica gel, 230 - 400 mesh; dichloromethane/methanol = 10/1) to obtain asiatic acid (1.5 g), madecassic acid (1.4 g) and mixture (2.0 g) of asiaticoside and madecassoside. The obtained mixture was dissolved in minimum amount of 60% methanol, in a water bath at 100℃, and then cooled at room temperature to give pure asiaticoside as needle-like crystalline. (m.p.: 230 - 240℃)

Separately, the extract (62 g) was dissolved in methanol (700 ml), and 5N sodium hydroxide solution(50ml) was added thereto, and the resultant mixture was heated under reflux for 10 hours. The reaction mixture was concentrated under reduced pressure, neutralized, filtered and dried to obtain a mixture (2, 43g) of asiatic acid and madecassic acid.

Example 2: Preparation of 3,23-O-Isopropylidene asiatic acid (3)

The mixture (12 g) of asiatic acid and madecassic acid, and p-toluenesulfonic acid (200 mg) were dissolved in anhydrous DMF (100

ml), and 2,2-dimethoxypropane (5 ml) was added thereto by injection. The resultant mixture was stirred at room temperature for 14 hours, and then neutralized and concentrated under reduced pressure to remove the solvent. After extracting, washing and drying, the residue was purified by column chromatography (dichloromethane:methanol = 30:1) to obtain 8.04 g of 3,23-O-isopropylidene asiatic acid (3).

IR (neat) : 3440, 1698, 1200 cm^{-1}

Mass (EI) : m/e 528 (M^+), 513 (M^+-Me), 482 (M^+-HCOOME), 452, 424, 407, 248, 203, 189, 133

^{1}H-NMR ($CDCl_3$) : δ 0.75, 1.04, 1.06, 1.09, 1.45, 1.46 (each s, 3H), 0.85 (d, 3H, J=6.4Hz), 0.95 (d, 3H, J=6.4Hz), 2.18 (d, 1H, J=11.2Hz), 3.32 (d, 1H, J=9.6Hz), 3.46, 3.51(ABq, 2H, J=10.8Hz), 3.78 (m, 1H), 5.24 (brt, 1H)

Example 3: Preparation of Methyl 3,23-O-isopropylideneasiatate (4)

3,23-O-Isopropylidene asiatic acid (3) (5 g) was dissolved in ethyl ether, and ethereal solution of diazomethane was slowly added dropwise thereto at 0℃. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure to remove ether, and the residue was purified by column chromatography (hexane:ethyl acetate = 3:1) to obtain 4.9 g of methyl 3,23-O-isopropylidene asiatate (4) (95%).

IR (neat) : 3466, 1724, 1201 cm-1

Mass (EI) : m/e 542 (M^+), 527 (M^+-Me), 482 (M^+-HCOOME), 483, 467, 451, 407, 262, 203, 189, 133

^{1}H-NMR ($CDCl_3$) : δ 0.66, 0.97, 1.00, 1.02, 1.40, 1.39 (each s, 3H), 0.79 (d, 3H, J=6.4Hz), 0.87 (d, 3H, J=6.0Hz), 2.15 (d, 1H), 3.25 (d, 1H,J=9.6Hz), 3.41 3.43 (ABq, 2H), 3.53 (s, 3H), 3.72 (m, 1H), 5.18 (brt, 1H)

Example 4: Preparation of 3,23-O-alkylidene asiatic acid (5)

① R_6=H, R_7=H

Dimethyl sulfoxide (2.5 eq.) and trimethylsilyl chloride (2.5 eq.) were added to THF with stirring. Asiatic acid (2) obtained above (2.53 g, 5.18 mmol) was added thereto, and the mixture was heated under reflux and argon atmosphere for 3 days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (dichloromethane:methanol = 20:1) to obtain 2.01 g of pale yellow solid (yield: 79.45%).

^{1}H NMR (300MHz, $CDCl_3$) δ 0.75, 1.05, 1.08, 1.12 (each s, 3H),
0.85 (d, 3H, J=6.18Hz), 0.95 (d, 3H, J=5.76Hz),
2.19 (d, 1H, J=10.9Hz), 3.04, 3.76 (ABq, 2H, J=10.11Hz),
3.23 (d, 1H, J=10.23Hz), 3.87 (dt, 1H, J=4.26Hz, 10.02Hz),
4.95 (d,d, 2H, J=5.9Hz), 5.24 (t, 1H)

② R_6=H, R_7=CH_3

Asiatic acid (255 mg, 0.52 mmol) obtained above was dried over p-toluenesulfonic acid under reduced pressure. Then the compound was dissolved in anhydrous THF, and $CH_3CH(OEt)_2$ (0.15 ml) was added dropwise thereto, and the resultant mixture was stirred at room temperature for 2 hours. To the reaction mixture, saturated solution of sodium carbonate was added by injection, and the solvent was removed by evaporation under reduced pressure. The residue was diluted with ethyl acetate, washed and dried, and purified by column chromatography (dichloromethane:methanol = 20:1) to obtain 178 mg of title compound (yield: 66.2%).

IR (neat) 2926, 1695 cm^{-1}

Mass (EI) m/e 514 [M^+]

^{1}H NMR (300MHz, $CDCl_3$) δ 5.14 (t, 1H), 4.64 (qt, 1H, J=4.92Hz),
3.75 (m, 1H), 3.63, 2.97 (ABq, 2H, J=10.1Hz),

3.17 (d, 1H, J=10.4Hz), 0.98, 0.95, 0.65 (each s, 3H),
0.85 (d, 3H, J=5,49Hz), 0.75 (d, 3H, J=6.39Hz)

③ R_6=H, R_7=C_6H_5

Excepting from substituting $C_6H_5CH(OMe)_2$ for $CH_3CH(OEt)_2$, the same procedure as Example 4② was performed (yield:32.1%).

IR (neat) 3437, 1696 cm^{-1}

Mass (EI) m/e 576 [M^+] 578

^1H NMR (300MHz, $CDCl_3$) δ 7.52~7.49 (m, 2H), 7.37~7.35(m, 3H),
5.53(s, 1H), 5.24(t, 1H), 3.90, 3.30(ABq, 2H, J=10.11Hz),
3.47(d, 1H, J=10.47Hz), 2.18 (d, 1H, J=11.46Hz), 1.19, 1.09,
4.07, 0.77 (each s, 3H), 0.93 (d, 3H, J=6.09Hz),
0.85 (d, 3H, J=6.33Hz)

④ R_6=CH_3, R_7=C_2H_5

Excepting from substituting $C_2H_5COCH_3$ for $CH_3CH(OEt)_2$, the same procedure as Example 4② was performed (yield:58.96%).

IR (neat) 3436, 1694 cm^{-1}

Mass (EI) m/e 542 [M^+]

^1H NMR (300MHz, $CDCl_3$) δ 5.18 (t, 1H), 3.68,
3.47 (ABq, 2H, J=4.26Hz), 3.48 (d, 1H, J=7.05Hz), 2.12(d,
1H,J=10.65Hz), 0.97, 0.89, 0.69 (each s, 3H)

⑤ R_6=CH_3, R_7=C_3H_7

Excepting from substituting $C_3H_7COCH_3$ for $CH_3CH(OEt)_2$, the same procedure as Example 4② was performed (yield:43.01%).

IR (neat) 3369, 2928, 1694 cm^{-1}

Mass (EI) m/e 558 [M^++2]

^1H NMR (300MHz, $CDCl_3$) δ 5.18 (t, 1H), 3. 79~3.75 (m, 1H),

3.18 (d, 1H, J=10.23Hz), 3.67, 2.98 (ABq, 2H, J=9.8Hz),
2.12 (d, 1H, J=10.65Hz), 1.05, 1.01, 0.98, 0.69 (each s, 3H),
0.88 (d, 3H, J=5.55Hz), 0.79 (d, 3H, J=6.39Hz)

⑥ R_6-R_7=-$(CH_2)_5$-

Excepting from substituting cyclohexanone for $CH_3CH(OEt)_2$, the same procedure as Example 4② was performed.

Mass (EI) m/e

^{1}H NMR (300MHz, $CDCl_3$) δ 0.77, 0.96, 1.07 (each s, 3H),
0.85 (d, 3H, J=6.33Hz), 2.18 (d, 1H, J=11.46Hz),
3.24 (d, 1H, J=9.51Hz), 3.41, 3.59 (ABq, 2H, J=10.47Hz),
3.76 (dt, 1H, J=8.54Hz), 5.23 (t, 1H)

Example 5 : Preparation of octyloxymethyl 3, 23-O-alkylidene asiatate(6)

① R_6=H, R_7=H

The compound 5(258.4mg, 0.52mmol) obtained in Example 4① above was dissolved in anhydrous dichloromethane. Diisopropylethylamine(0.18ml) was added thereto and stirred at room temperature for 10 minutes. At 0℃, chloromethyloctyl ether(0.1ml) was added dropwise thereto and stirred for 5 minutes. Methanol was added thereto and the residue was refined by column chromatography (dichloromethane:methanol=30:1) to obtain 138mg of white solid (yield: 41.6%).

^{1}H NMR (400MHz, $CDCl_3$) δ 0.76, 1.05, 1.09, 1.13 (each s, 3H),
0.88 (d, 3H, J=5.6Hz), 0.95 (d, 3H, J=6.36Hz),
2.25 (d, 1H, J=10.8Hz), 3.04, 3.76 (ABq, 2H, J=10.0Hz),
3.22 (d, 1H, J=10.8Hz), 3.58 (m, 2H), 4.94 (d,d, 2H, J=6.0Hz),
5.21, 5.24 (ABq, 2H, J=5.88Hz), 5.26 (t, 1H)

② R_6=H, R_7=CH_3

Excepting from substituting compound 5 obtained in Example 4② for compound 5 obtained in Example 4① above, the same procedure as Example 5① was performed.

IR (neat) 3481, 2927, 1732 cm^{-1}

Mass (EI) m/e 656 [M^+]

^{1}H NMR (300MHz, $CDCl_3$) δ 5.22 (t, 1H), 5.20,
5.17 (ABq, 2H,J=6.21Hz), 4.69 (qt, 1H, J=4.95Hz),
3.84~3.77 (m, 1H), 3.69, 3.03(ABq, 2H, J=10.07Hz), 3.55 (m, 2H),
2.22 (d, 1H, J=11.16Hz), 1.05, 1.00, 0.95, 0.72 (each s, 3H),
0.84 (d, 3H, J=2.55Hz), 0.82 (d, 3H, J=2.19Hz)

③ R_6=H, R_7=C_6H_5

Excepting from substituting compound 5 obtained in Example 4③ for compound 5 obtained in Example 4① above, the same procedure as Example 5① was performed (yield:23.8%).

IR (neat) 3697, 1730 cm^{-1}

Mass (EI) m/e 719 [M^++1]

④ R_6=CH_3, R_7=C_2H_5

Excepting from substituting compound 5 obtained in Example 4④ for compound 5 obtained in Example 4① above, the same procedure as Example 5① was performed (yield:58.96%).

IR (neat) 3469, 1733 cm^{-1}

Mass (EI) m/e 684 [M^+]

^{1}H NMR (300MHz, $CDCl_3$) δ 5.16 (t, 1H), 5.14,
5.11(ABq, 2H, J=6.29Hz), 3.68(m,1H), 3.48 (m, 2H,),
3.24 (d, 1H, J=9.57Hz), 2.16(d, 1H,J=11.5Hz), 1.00, 0.96, 0.91,

0.66 (each s, 3H), 0.84(d,1H,J=5.55Hz), 0.76(d,1H,J=5.73Hz)

⑤ R_6=CH_3, R_7=C_3H_7

Excepting from substituting compound 5 obtained in Example 4⑤ for compound 5 obtained in Example 4① above, the same procedure as Example 5① was performed (yield:80.2%).

IR (neat) 3468, 2927, 1729 cm^{-1}

Mass (EI) m/e 698 [M^+]

^{1}H NMR (400MHz, $CDCl_3$) δ 5.26~5.20 (m, 2H), 5.10 (t, 1H), 3.87~3.84 (m, 1H), 3.60~3.56 (m, 2H), 2.27 (d, 1H), 1.08, 1.07, 1.03, 0.76 (each s, 3H), 0.94 (d, 3H, J=5.84Hz), 0.87 (d, 3H, J=5.4Hz)

⑥ R_6-R_7 = -$(CH_2)_5$-

Excepting from substituting compound 5 obtained in Example 4⑥ for compound 5 obtained in Example 4① above, the same procedure as Example 5① was performed (yield: 34%).

Mass (EI) m/e 710 [M^+], 667, 596, 567, 522, 521

^{1}H NMR (400MHz, $CDCl_3$) δ 0.75, 0.95, 1.03 (each s, 3H), 0.87 (d, 3H, J=5.86Hz), 1.09 (d, 3H, J=3.9Hz), 2.10 (d, 1H, J=4.40Hz), 3.35 (d, 1H, J=9.77Hz), 3.48, 3.52 (ABq, 2H, J=11.24Hz), 3.58 (m, 2H), 3.8 (m, 1H), 5.21, 5.24 (dd, 2H, J=5.86Hz), 5.26 (t, 1H)

Example 6 : Preparation of methyl 3, 23-O-isopropylidene-2-O-[(methylthio)thiocarbonyl]asiatate(7)

Sodium hydride(60% dispersion of inorganic oil, 18.3 mg, 0.46 mmole), imidazole(2 mg) and tetrahydrofuran(2 ml) were added to methyl 3, 23-O-isopropylidene asiatate (4) (50 mg, 0.092 mmole) and the

resultant mixture was stirred for 30 minutes. Carbon disulfide(0.2 ml, excessive amount) was added thereto and refluxed for 2 hours. Methyl iodide (0.1 ml, excessive amount) was added thereto and heated under reflux again for 1 hour. The reactant mixture was treated with water and the solvent was removed under reduced pressure. After extracting, washing and drying the residue was refined by column chromatography(hexane:ethyl acetate = 10:1) to obtain 56 mg of white solid (yield : 96%).

IR (neat) : 1723, 1233, 1057 cm^{-1}

^1H NMR ($CDCl_3$) δ 5.78(1H,m), 5.24(1H,bt), 3.80(1H,d,J=10Hz), 3.60(3H,s), 3.54, 3.58(2H,dd,J=7.2Hz), 2.51(3H,s), 2.23(1H,d,J=11.2Hz), 0.94(3H,d, J=5.2Hz), 0.84(3H,d,J=6Hz), 0.73, 1.09, 1.11, 1.14, 1.41, 1.45 (each 3H,s).

Example 7 : Preparation of methyl 2-deoxy-3, 23-O-isopropylidene asiatate(8)

A catalytic amount of AIBN and benzene(10ml) were added to xanthate compound (7)(202mg, 0.32mmole) obtained above. Tributyltin hydride(0.26ml, 0.96mmole) was added thereto with the resultant heated under reflux and stirred for 1 hour and a half. The reactant mixture was concentrated under reduced pressure and the solvent was removed. The obtained residue was refined by column chromatography(hexane:ethyl acetate = 10:1) to obtain 168 mg of white solid (yield : 100%). The product was recrystallized with hexane to yield needle-like crystalline.

IR (neat) : 1724 cm^{-1}

MS (EI) : 527(M^++1), 512, 407, 262, 203, 133.

^1H NMR ($CDCl_3$) δ 5.25(1H,bt), 3.60(3H,s), 3.52(1H,t), 3.44, 3.54(2H,dd,J=10Hz), 2.23(1H,d,J=11.2Hz), 0.94 (3H, d, J=5.6Hz), 0.86(3H,d,J=6.4Hz), 0.73, 0.97, 1.07, 1.09, 1.42, 1.45(each 3H,s)

Example 8 : Preparation of methyl 2-deoxyasiatate(9)

Tetrahydrofuran(10 ml) and 1N HCl solution(1ml) were added to compound(8) (460mg, 0.87mmole) obtained above and stirred at room temperature for 5 hours. The solvent was totally removed by distillation under reduced pressure. The obtained residue was refined by column chromatography(hexane:ethyl acetate = 3:2) to obtain 402 mg of white solid (yield : 95%). The crude product obtained was recrystallized with ethyl acetate to yield needle-like crystalline.

IR (neat) : 3400, 1724 cm^{-1}

MS (EI) : 486(M^+), 426, 262, 203, 133

Example 9 : Preparation of 2-deoxyasiatic acid (10)

LiI-$3H_2O$ (450mg, 2.39mmole) and 2,4,6-colidine(5ml) was added to methyl 2-deoxyasiatate (9) (38mg, 0.78mmole) and heated under reflux for 10 hours. The flask was covered with aluminium foil to block light during reflux. The reactant solution was concentrated under reduced pressure to remove collidine. The obtained residue was refined by column chromatography(dichloromethane:methanol=20:1) to obtain pale yellow solid (yield : 99%). The product obtained was recrystallized with methanol to yield 280 mg of needle-like crystalline(yield : 76%).

IR (KBr) : 3436, 1693 cm^{-1}

MS (EI) : 472(M^+), 426, 248, 203, 133

^1H NMR ($CDCl_3$ + pyridine-d_5) δ 5.21(1H,bt,J=2.8Hz,3.6Hz), 3.60(1H,t,J=7.2Hz,8.2Hz), 3.36, 3.70 (2H,dd,J=10.0Hz), 2.21(1H,d,J=11.2Hz).

Example 10 : Preparation of 2-deoxy-3, 23-O-isopropylidene asiatic acid (11)

Excepting from substituting compound 10 for the mixture of

asiatic acid and madecassic acid, the same procedure as Example 2 was performed (yield:59.9%).

IR (neat) 2928, 1697 cm^{-1}

^1H NMR (400MHz, $CDCl_3$) δ 5.25 (d, 1H), 3.52 (t, 1H), 2.17 (d, 1H), 1.44, 1.40, 1.10, 1.04, 0.98, 0.78 (each s, 3H), 0.95 (d, 3H, J=6.4Hz), 0.87 (d, 3H, J=6.4Hz)

Example 11 : Preparation of octyloxymethyl 2-deoxy-3, 23-O-isopropylidene asiatate(12, R_5=octyloxymethyl)

Excepting from substituting compound 11 for compound 5 in Example 5① above, the same procedure as Example 5① was performed (yield:53.9%).

IR (neat) 2929, 1733 cm^{-1}

Mass (EI) m/e 654 [M^+]

^1H NMR (500MHz, $CDCl_3$) δ 5.17 (t, 1H), 5.14, 5.12 (ABq, 2H, J=6.02Hz), 3.49~3.48 (m, 2H), 3.46, 3.34(ABq,2H,J=6.17Hz), 2.15 (d, 1H), 1.35, 1.32, 1.01, 0.96, 0.67 (each s, 3H), 0.87 (d, 3H, J=7.04Hz),

Example 12 : Preparation of ethyloxymethyl 2-deoxy-3, 23-O-isopropylidene asiatate(12, R_5=ethoxymethyl)

Excepting from substituting compound 11 for compound 5 in Example 5① and substituting chloromethylethyl ether for chloromethyloctyl ether, the same procedure as Example 5① was performed (yield:46%).

IR (neat) 2929, 1733 cm^{-1}

Mass (EI) m/e 570 [M^+]

^1H NMR (500MHz, $CDCl_3$) δ 5.16 (t, 1H), 5.16 (s, 2H), 3.60, 3.58(ABq, 2H, J=1.36Hz), 3.45~3.35 (m, 3H), 2.15 (d, 1H),

1.45, 1.38, 1.34, 1.04, 0.98, 0.70 (each s, 3H),
0.88 (d, 3H, J=6.32Hz), 0.79 (d, 3H, J=2.24Hz)

Example 13 : Preparation of tetrahydropyranyl 2-deoxy-3, 23-O-isopropylidene asiatate (12, R_5=2-tetrahydropyranyl)

Compound 11(133mg, 0.26mmol) and pyridinium paratoluene sulfonate(catalytic amount) were dissolved in anhydrous dichloromethane. Dihydropyrane(0.07ml) was added dropwise thereto and stirred at room temperature for 40 hours. The resultant was neutralized and the solvent was removed under reduced pressure. After extracting, washing and drying, the residue was refined by column chromatography (hexane:ethyl acetate=8:1) to 73mg of compound(12, R_5=2-tetrahydropyranyl) (yield:47.2%).

IR (neat) 2945, 1733 cm^{-1}

^1H NMR (400MHz, $CDCl_3$) δ 5.96(t, 1/2H), 5.92(t, 1/2H),
5.28(t, 1/2H), 5.26 (t, 1/2H), 3.88 (t, 1H), 3.67 (t, 1H),
3.52 (t, 2H), 3.46 (t, 2H), 1.45, 1.42, 1.11, 1.05,
0.96 (each s, 3H), 0.87 (d, 3H, J=6.4Hz)

Example 14 : Preparation of methyl 2-O-octyloxymethyl-3,23-O-isopropylidene asiatate (13)

Excepting from substituting compound 4 for compound 5 in Example 5①, the same procedure as Example 5① was performed.

IR (neat) 2927, 1728 cm^{-1}

Mass (EI) m/e 684 [M^+]

^1H NMR (500MHz, $CDCl_3$) δ 5.18 (t, 1H), 4.73,
4.62 (ABq, 2H, J=6.72Hz), 3.70~3,65 (m, 1H), 3.53 (s, 3H),
3.35 (d, 1H, J=9.76Hz), 1.36, 1.33, 1.02, 1.01, 0.96,
0.66 (each s, 3H), 0.87 (d, 3H, J=6.18Hz), 0.79 (d, 3H, J=6.46Hz)

Example 15 : Preparation of methoxymethyl 3, 23-O-isopropylidene asiatate (14, R_5=methoxymethyl)

Excepting from substituting compound 3 for compound 5 in Example 5① and substituting chloromethylmethyl ether for chloromethyloctyl ether, the same procedure as Example 5① was performed (yield:19%).

mp. 104-112℃

^{1}H NMR (300MHz, $CDCl_3$): δ 0.77, 1.04, 1.08, 1.11, 1.45, 1.46(each s, 3H), 0.87 (d, 3H, J=6.3Hz), 0.96(d, 3H, J=5.7Hz), 2.27 (d, 1H, J=11.1Hz), 3.32 (d, 1H, J=9.6Hz), 3.45 (s, 3H), 3.47 (d, 1H, 9.6Hz), 3.55 (d, 1H, 9Hz), 3.79 (m, 1H), 5.17 (d, 1H, 6Hz), 5.20 (d, 2H, J=6Hz), 5.28 (t, 1H, J=3.5Hz)

IR (KBr) cm^{-1} 3500, 2950, 1740, 1450, 1380, 1065, 925, 860

$[\alpha]_o^{23} = +10.4^\circ$ (c=0.2, $CHCl_3$)

Example 16 : Preparation of ethoxymethyl 3, 23-O-isopropylidene asiatate (14, R_5=ethoxymethyl)

Excepting from substituting compound 3 for compound 5 in Example 5① and substituting chloromethylethyl ether for chloromethyloctyl ether, the same procedure as Example 5① was performed (yield:46%).

IR (neat) : 3468, 1734 cm^{-1}

MS (EI) m/z : 586 (M^+)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (t,1H), 5.23 (s,2H), 3.74 - 3.82 (m,1H), 3.66 (q,2H,J=7.6Hz), 3.53, 3.44 (ABq, 2H), 3.32 (d, 1H, J=9.6Hz), 2.25 (d , 1H), 1.46, 1.44, 1.10 (ABq, 2H), 1.07, 1.03, 0.76 (each s, 3H), 1.22 (t, 3H, J=6.8Hz), 0.95 (d, 3H, J=5.6Hz), 0.86 (d, 3H, J=6.4Hz)

Example 17 : Preparation of methoxyethoxymethyl 3, 23-O-isopropylidene asiatate (14, R_5=methoxyethoxymethyl)

Excepting from substituting compound 3 for compound 5 in Example 5① and substituting methoxyethoxymethyl chloride for chloromethyloctyl ether, the same procedure as Example 5① was performed (yield:25%).

mp. 76-79℃

^{1}H NMR (300MHz, $CDCl_3$): δ 0.77, 1.04, 1.08, 1.11, 1.45, 1.46 (each s, 3H), 0.86 (d, 6.3Hz, J=3Hz), 0.96 (d, 3H, J=5.7Hz), 2.2-0.9 (m, 21H), 2.26 (d, 1H, J=10.2Hz), 3.32 (d, 1H, J=9.6Hz), 3.39 (s, 3H), 3.47 (d, J=9.0Hz), 3.52 (d, 1H, J=9.0Hz), 3.55 (t, 2H, J=5.1Hz), 3.77 (m, 1H), 3.77 (t, 2H, J=5.1Hz), 5.26 (t, 1H, J=3.6Hz), 5.28 (s, 2H)

IR (KBr) cm^{-1} 3500, 2950, 1725, 1450, 1380, 1070, 940, 860

$[\alpha]_o^{24}$ = +38.7° (c=0.1, $CHCl_3$)

Example 18 : Preparation of methoxymethyl 2-O-acetyl-3, 23-O-isopropylideneasiatate(15, R_5=methoxymethyl)

Compound(14)(R_5=methoxymethyl, 139mg, 0.24mmol) obtained above was dissolved in pyridine and stirred. Acetic anhydride(0.04ml, 0.38mmol) was added thereto and stirred for 2 days. The resultant was concentrated under reduced pressure , washed, dried and refined by column chromatography (dichloromethane:methanol=30:1) to 75mg of white solid (yield:52%).

mp. 110-115℃

^{1}H NMR (300MHz, $CDCl_3$): δ 0.77, 1.09, 1.11, 1.12, 1.41, 1.43, 2.01 (each s, 3H), 0.86 (d, 3H, J=6.3Hz), 0.95 (d, 3H, J=6Hz), 2.27 (d, 1H, J=10.8Hz), 3.45 (s, 3H), 3.50 (d, 1H, J=9.6Hz), 3.52 (d, 1H, J=9.6Hz), 3.56 (d, 3H, J=9Hz), 5.0 (m, 1H), 5.17 (d, 1H, J=6Hz), 5.20 (d, 1H, J=6Hz), 5.27 (t, 1H, J=3.5Hz)

IR (KBr) cm^{-1} 2950, 2740, 1450, 1240, 1080, 1025, 950, 800

$[\alpha]_o^{24}$ = +43.6° (c=0.1, $CHCl_3$)

Example 19 : Preparation of ethoxymethyl 2-O-acetyl-3, 23-O-isopropylideneasiatate(15, R_5=ethoxymethyl)

Excepting from substituting compound 14 (R_5=ethoxymethyl) obtained for compound 14 (R_5=methoxymethyl) used in Example 18, the same procedure as Example 18 was performed (yield:91%).

mp. 136-137℃

^{1}H NMR (300MHz, $CDCl_3$): δ 0.85 (d, 3H, J=6.1Hz), 0.95 (d, 3H, J=5.7Hz), 1.01, 1.06, 1.08, 1.41, 1.43, 2.01 (each s, 3H), 0.9-2.2 (m, 20H), 1.21 (t, 7.3Hz), 2.26 (d, 1H, 11.1Hz), 3.48 (d, 1H, J=9Hz), 3.53 (d, 1H, J=9Hz), 3.54 (d, 1H, J=10.7Hz), 3.66 (q, 2H, J=7.3Hz), 5.00 (dt, 1H, 4.3, 10.7Hz), 5.23 (s, 2H), 5.26 (t, 1H, J=4.2Hz)

$[\alpha]_o^{24}$ = -0.66° (c=0.34, CCl_4)

Example 20 : Preparation of ethoxymethyl 2-O-ethoxymethyl-3, 23-O-isopropylideneasiatate (16)

Excepting from substituting compound 3 for compound 5 obtained in Example 5① above, and substituting chloromethylethyl ether for chloromethyloctyl ether , the same procedure as Example 5① was performed (yield:19%).

mp. 68-70℃

^{1}H NMR (300MHz, $CDCl_3$): δ 0.86 (d, 3H, J=6.3Hz), 0.95 (d, 3H, J=5.7Hz), 0.80, 1.05, 1.10, 1.41, 1.51 (each s, 3H), 0.9-2.2 (m, 20H), 1.22 (t, 3H, J=7.2Hz), 2.26 (d, 1H, J=11.1Hz), 3.35 (d, 1H, J=9Hz), 3.39 (d, 1H, J=9Hz), 3.46 (d, 1H, J=9.6Hz), 3.60 (q, 2H, J=7.2Hz), 3.76 (q, 2H, J=7.2Hz),

3.80 (dt, 1H, 4.2, 9.6Hz), 4.67 (s, 2H), 5.24 (s, 2H),
5.27 (t, 1H, J=3.6Hz)

IR (KBr) cm^{-1} 2950, 1715, 1450, 1380, 1020, 925, 860

$[\alpha]_o^{24} = +33.1^\circ$ (c=0.1, $CHCl_3$)

Example 21 : Preparation of benzyloxymethyl 3, 23-O-diacetyl asiatate (17)

Excepting from substituting compound 3 for compound 5 obtained in Example 5① and substituting chloromethylbenzyl ether for chloromethyloctyl ether , the same procedure as Example 5① was performed and then synthesized through acetylization (yield:45%).

^{1}H NMR (300MHz, $CDCl_3$): δ 0.75, 0.85, 0.99, 1.10, 2.04, 2.09 (each s, 3H),
0.89 (d, 3H, J=6.3Hz), 0.9-2.2 (m, 21H), 2.27 (d, 1H, J=12.9Hz),
3.57 (d, J=11.7Hz), 3.83 (d, J=11.7Hz), 3.90 (dt, 1H, 3.9, 10.2Hz),
4.68 (s, 2H), 5.04 (d, 1H, J=10.2Hz), 5.28 (t, 1H, J=3.6Hz),
5.32 (s, 3H), 7.34 (s, 5H)

IR (neat) cm^{-1} 2950, 2740, 1450, 1380, 1065, 925, 860, 800

$[\alpha]_o^{25} = +25.25^\circ$ (c=0.1, $CHCl_3$)

Example 22 : Preparation of methyl 2-O-methanesulfonyl-3, 23-O-isopropylideneasiatate (18)

Methyl 3, 23-O-isopropylidene asiatic acid (4) (354.7mg, 0.65mmole) was dissolved in dichloromethane(15ml). Triethyl amine(82.4mg, 0.72mmole) and methanesulfonyl chloride(99.2mg, 0.98mmole) were added thereto and stirred at 0℃ for 3 hours under nitrogen atmosphere. After the reaction was finished, the solvent was removed. After extracting, washing and drying, the residue was refined by column chromatography (hexane:ethyl acetate=2:1) to 380mg of pure

compound (18) as white solid (yield:93%).

^{1}H NMR ($CDCl_3$) δ 5.24(1H, m), 4.69-4.62 (1H, m), 3.60 (3H, s), 3.57 (1H, d ,J=10.5Hz), 3.53 (1H, d, J=10.5Hz), 3.49 (1H, d, J=10.5Hz), 3.01 (3H, s), 2.26-2.20 (1H, m), 2.23(1H, bs), 1.44 (3H, s), 1.40 (3H, s), 1.11 (3H, s), 1.09 (3H, s), 1.07 (3H, s), 0.94 (3H, d, J=6.0Hz), 0.85 (3H, d, J=7.0Hz), 0.72(3H,s)

Example 23 : Preparation of methyl 2-O-methanesulfonyl asiatate (19)

The compound(18) (1.2g, 1.92mmole) obtained above was dissolved in methanol(30ml). p-toluenesulfonic acid(480mg, 2.52mmole) was added thereto and refluxed for 10 minutes under nitrogen atmosphere. The reactant was neutralized, extracted, washed, dried and refined by column chromatography (hexane:ethyl acetate=1:1) to obtain 1.06g of pure compound (19) as colorless oil(yield : 94%).

^{1}H NMR ($CDCl_3$) δ 5.24 (1H, m), 4.77-4.74 (1H, m), 3.69 (1H, d, J=10.5Hz), 3.61 (3H,s), 3.44 (1H, d, J=10.5Hz), 3.70 (1H, bs), 3.10 (3H, s), 1.08 (3H, s), 1.07 (3H, s), 0.95 (3H, s), 0.94 (3H, d, J=5.1Hz), 0.85 (3H, d, J=6.5Hz), 0.74 (3H, s)

Example 24 : Preparation of methyl 2,3-epoxyasiatate (20)

The compound(19) (2.78g, 4.77mmole) obtained above was dissolved in methanol(60ml). Potassium carbonate(1.32g, 9.53mmole) was added thereto and stirred at room temperature for 3 days under nitrogen atmosphere. After the reaction was finished, solvent was removed. After extracting, washing and drying, the residue was refined by column chromatography (hexane : ethyl acetate=2:1) to obtain 2.05g of pure compound (20) as white solid (yield : 89%).

m.p. : 230~234℃

IR (KBr) : 3400, 2920, 1730, 1430, 1450, 1200, 1040 cm^{-1}

^1H NMR ($CDCl_3$) δ 5.27 (1H, m), 3.60 (3H, s), 3.56 (1H, m), 3.31 (1H, m), 3.27 (1H,m), 3.11 (1H, d, J=4.0Hz), 1.12 (3H, s), 1.6 (3H, s), 0.96 (3H, s), 0.94 (3H, d, J=5.1Hz), 0.86 (3H, d, J=6.4Hz), 0.74 (3H, s)

Example 25 : Preparation of methyl 2 β -iodo-2-deoxyasiatate(21)

Compound 20(24.5mg, 0.05mmol), LiI · $3H_2O$(98mg, 10.3eq) were dissolved in THF(5ml). AcOH(0.5ml) was added thereto with stirring, and the resultant was reacted for 1 day under argon atmosphere. The resultant was diluted with water, extracted with ethyl acetate, washed with brine and 10% $Na_2S_2O_3$ solution, dried, and refined by column chromatography(hexane:ethyl acetate = 3:1) to obtain 16.5mg of colorless solid (yield: 53.3%).

^1H NMR (300MHz, $CDCl_3$): δ 0.74, 0.85, 1.02, 1.08 (each s, 3H), 0.86 (d, 3H, J=6.3Hz), 0.94 (d, 3H, J=5.13Hz), 2.24 (d, 1H, J=11.2Hz), 3.42, 3.72 (ABq, 2H, J=12.7Hz), 3.60 (s, 3H), 4.57 (dt, 1H), 5.25 (t, 1H)

Mass (EI) m/e 612 [M^+], 552, 467, 407, 349

Example 26 : Preparation of 3,23-O-methylidene-2-oxoasatic acid(22)

Compound 22(1.1g 2.2mmole) and pyridinium dichromate(0.83g, 2.2mmole) were dissolved in anhydrous dichloromethane. Acetic anhydride (0.62ml) was added thereto and heated under reflux for 2 hours. The reactant was diluted with ethyl acetate, filtrated and refined by column chromatography (dichloromethane : methanol = 20 : 1) to obtain compound 23(0.32g, yield 29.2%)

^1H NMR (300MHz, $CDCl_3$) δ 0.75, 1.02, 1.07, 1.13 (each s, 3H), 0.95 (d, 3H, J=5.9Hz), 0.85 (d, 3H, J=6.3Hz), 2.11-2.21 (m, 2H), 2.39 (d, 1H, J=12.7Hz),

3.42, 3.84 (ABq, 2H, J=10.4Hz), 4.10 (s, 1H), 4.69, 5.20 (ABq, 2H, J=5.9Hz), 5.23 (t, 1H)

Example 27 : Preparation of Octyloxymethyl 3,23-O-methylidene-2-oxoasiatate(23)

Except from substituting compound 22 for compound 5 used in Example 5①, the same procedure as Example 5① was performed(yield : 44%).

^{1}H NMR (300MHz, $CDCl_3$) δ 0.78, 1.02, 1.10, 1.14 (each s, 3H), 0.87 (d, 3H, J=7.3Hz), 0.95 (d, 3H, J=5.9Hz), 2.13, 2.40 (ABq, 2H, J=12.7Hz), 2.27 (d, 1H, J=11.5Hz), 3.42, 3.84 (ABq, 2H, J=10.1Hz), 3.58 (dt, 2H, J=5.6Hz), 4.10 (s, 1H), 4.69, 5.24 (ABq, 2H, J=6.1Hz), 5.20-5.25 (m, 2H), 5.25 (t, 1H)

Experimental Example 1: Effect of the compounds according to the present invention on treating wound

Formulation : Ointment ointment is ≠ from our gel

The asiatic acid derivative (200 mg) according to the present invention was accurately weighed and placed in a 20 ml syringe. Propylene glycol (6 g), glycol stearate (3 g) and white petrolatum (1 g) were accurately weighed and added thereto. The content of the syringe was completely melted in a water bath at 80℃, and stirred for about 5 minutes so that the active component could be homogeneously dispersed in three kinds of vehicles mentioned above. Separately, purified water (10g) warmed to 80℃ was placed in another syringe. The above two syringes were connected by a threeway connector, and injecting from both side was repeated about 20 times to homogenize the content. The homogenized content was put into a vessel and slowly solidified at room temperature.

però il nostro gel è solo sale dell'ac. asiatico o madecassico ed H_2O

Experimental method

In order to examine the effect of newly systhesized asiatic acid derivatives, asiatic acid, madecassic acid and asiaticoside isolated from natural substance on treating wound, experimental wound have been made on rats, and the results have been watched. Among several measuring processes for wound-treating effect, which are based on the logic that the wound or the lesion owing to necrosis is treated by reproduction of tissue such as granulation, measuring of tensile strength is due to the fact that the tensile strength increases constantly until the recovering site becomes open again. In the measurement, the strength up to the point when the wounded site becomes open is measured, while both sides of the wound are pulled. It is known that the measuring of tensile strength reflects the quality and rate of reproduction in case of incised wound very well.

In Table 1, the effect of synthesized asiatic acid derivatives and that of titrated extracts of *Centella asiatica* (TECA), which is the main component of commercially available madecassol ointment, on treating wound were examined and compared, by using measurement of tensile strength.

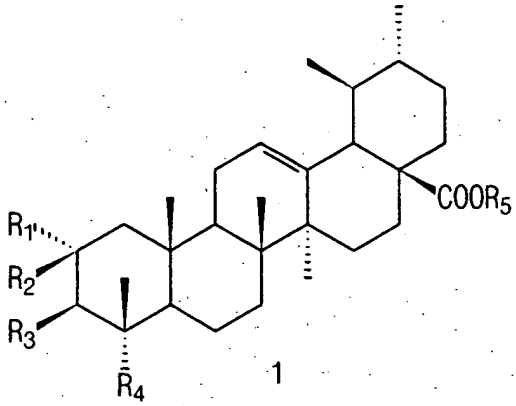
Table 1. Effect of novel asiaticoside derivatives on treating wound

Compounds	Tensile strength (g ± S.E.)	Variation
Compound 6 (R_6=H, R_7=H)	274.44 ± 35.97	20.2
Compound 6 (R_6=H, R_7=CH_3)	241.25 ± 22.32	5.7
Compound 6 (R_6=H, R_7=C_6H_5)	237.78 ± 22.21	4.1
Compound 6 (R_6=CH_3, R_7=C_2H_5)	212.22 ± 25.23	-7.1
Compound 6 (R_6=CH_3, R_7=C_3H_7)	235.56 ± 26.76	3.2
Compound 6 (R_6-R_7=-$(CH_2)_5$-)	237.5 ± 27.66	4.0
TECA	228.33 ± 15.53	
Compound 12 (R_5=$CH_2C_8H_{17}$)	310.00 ± 37.08	20.78
Compound 12 (R_5=$CH_2OC_2H_5$)	248.89 ± 22.02	-3.03
Compound 12 (R5=tetrahydropyranyl)	362.22 ± 27.57	41.12
Compound 13	257.70 ± 27.02	0.40
TECA	256.67 ± 24.19	

As can be seen from the Experimental Examples described above, the asiatic acid derivatives according to the present invention showed excellent effect on treating wound.

CLAIMS

1. An asiatic acid derivative represented by general formula 1, or pharmaceutically acceptable salt or ester thereof.



1

wherein, R_1 represents hydrogen, hydroxy group which may be protected by acetyl or benzyl group, methanesulfonyloxy, (methylthio)thiocarbonyloxy, a halogen, ethoxymethyloxy or octyloxymethyloxy group; R_2 represents hydrogen or hydroxy group; R_1 and R_2 may form an oxo group; R_3 represents hydroxy group which may be protected by acetyl or benzoyl group, or hydrogen; R_2 and R_3 may form an epoxy group; R_4 represents hydroxymethyl group which may be protected by acetyl or benzoyl group; R_3 and R_4 may form -$OC(R_6)(R_7)OCH_2$- [wherein, R_6 is hydrogen, a lower alkyl group having 1 to 4 carbon atoms, or phenyl group, R_7 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms or phenyl group, and R_6 and R_7 may form -$(CH_2)_5$-]; R_5 represents hydrogen, a lower alkyl group having 1 to 4 carbon atoms, an alkoxymethyl group having 1 to 4 carbon atoms, octyloxymethyl, methoxyethoxymethyl, benzyloxymethyl or 2-tetrahydropiranyl group,

2. A medicine for treating wound, which comprises an asiatic acid derivative represented by general formula 1, or pharmaceutically acceptable salt or ester thereof according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00239

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 C 62/32; C 07 D 319/08; A 61 K 31/19; C 07 C 69/757

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 C 62/32, 69/757; C 07 D 319/08; A 61 K 31/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: G-DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/17 819 A1 (DONG KOOK) 13 June 1996 (13.06.96), claims.	1,2
X	Chemical Abstracts, Vol. 125, No. 7, 12 August 1996 (Columbus, Ohio, USA), page 706, abstract No. 81911x, C. FOURNEAU et al. "Triterpenes from Prunus africana bark" & Phytochemistry 1996, 42(5), 1391-1393.	1
X	Chemical Abstracts, Vol. 122, No. 15, 10 April 1995 (Columbus, Ohio, USA), page 874, abstract No. 185527f, N. OKADA et al. "A triterpene, its manufacture and cancer inhibitors containing triterpenes" & Jpn. Kokai Tokkyo Koho JP 06-329590.	1,2
X	Chemical Abstracts, Vol. 118, No. 21, 24 May 1993, (Columbus, Ohio, USA), pages 536,537, abstract No. 209385d, C. HUANG et al. "Isolation and identification of a new triterpene from Actinidia eriantha Benth." & Tianran Chanwu Yanjiu Yu Kaifa 1992, 4(3), 27-30.	1
X	Chemical Abstracts, Vol. 109, No. 15, 10 October 1998 (Columbus, Ohio, USA), page 390, abstract No. 125856j,	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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International application No.
PCT/KR 97/00239

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	C. HUANG et al. "Isolation and identification of two new triterpenes from Actinidia eriantha" & Yunnan Zhiwu Yanjiu 1988, 10(1) 93-100.	
X	Chemical Abstracts, Vol. 102, No. 7, 18 February 1985 (Columbus, Ohio, USA), page 351, abstract No. 59349y, T.KIKUCHI et al. "Studies on the constituents of medicinal and related plants in Sri Lanka. I. New triterpenes from Hedyotis lawsoniae" & Chem. Pharm. Bull. 1984, 32(10), 3906-11.	1
X	Chemical Abstracts, Vol. 100, No. 21, 21 May 1984 (Columbus, Ohio, USA), page 353, abstract No. 171516k, J.SAKAKIBARA et al. "Terpenoids of Rhododendron japonicum" & Phytochemistry 1983, 22(11), 2535-5.	1
X	Chemical Abstracts, Vol. 76, No. 9, 28 February 1982 (Columbus, Ohio, USA), page 2, abstract No. 41801z, L.F.CHASSEAUD et al. "Metabolism of asiatic acid, madecassic acid, and asiaticoside in the rat." & Arzneim.-Forschung 1971, 21(9), 1379-84.	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 97/00239

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9617819	13-06-96	AU A1 39955/95	26-06-96
		DE T 19581854	04-12-97
		FR A1 2727678	07-06-96
		GB A0 9710644	16-07-97
		GB A1 2309695	06-08-97

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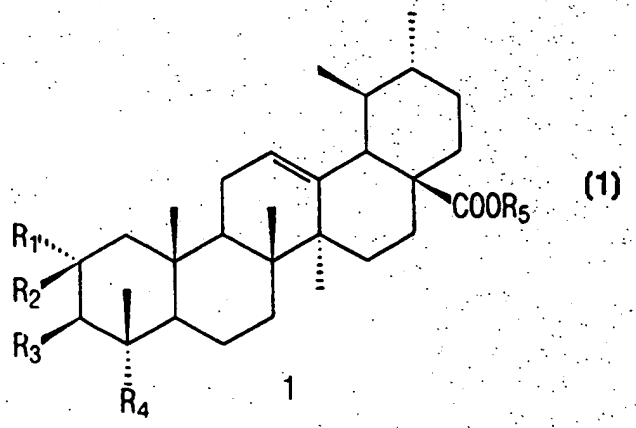
(54) Title: ASIATIC ACID DERIVATIVES AND MEDICINES FOR TREATING WOUNDS, WHICH CONTAINS THE SAME

(57) Abstract

The present invention relates to asiatic acid derivatives represented by formula (1), and medicines for treating wounds, which contains the same as an active component.



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